REMARKS

Reconsideration and withdrawal of the objections to the specification and rejections of the claims, in view of the remarks and amendments herein, is respectfully requested. Claims 1, 4, 21, 43, and 46 are amended, claims 28 and 54 are canceled, and claims 61-62 are added; as a result, claims 1-7, 9-27, 29-46, 48-53, 55-59, and 61-62 are now pending in this application. The amendments are intended to advance the application and are not intended to concede to the correctness of the Examiner's position or to prejudice the prosecution of the claims present prior to amendment, which claims are in a continuing application of the above-identified pending application.

The specification is amended at pages 19, 20, 54, and 84 to address objections thereto at pages 3-4 of the Office Action.

The Objections to the Specification

The specification was objected to because 1) the functional abilities of doxorubicin, doxyrubicin and DOXIL® are not identical and so each agent should be clearly and explicitly identified throughout the disclosure; 2) Miglyol is a registered trademark name but that term is not identified accordingly in the specification; 3) the unit DF* is not defined; 4) none the figure legends for Figures 4A-E identify data from the combined use of LLnL and doxorubicin; 5) the specification does not disclose the data presented in Figure 6C, panels A-C of Figure 8, panels A-D of Figure 9, panels A-B of Figure 10, and panels A-D of Figure 11; 6) the specification does not adequately identify the "DOX" compound whose effects are graphed in Figure 7, Figure 13, Figure 17, Figure 18, and Figure 19; and 7) the specification discloses the data presented in Figure 13 as "right panel" and "left panel", however, there are no "right" or "left" panels.

The amendments to the specification address items 2) and 3) above.

With regard to "doxorubicin" and "doxyrubicin," Applicant noted in the Amendment filed on August 14, 2007 that those terms are synonymous. Moreover, one of ordinary skill in the art would recognize that those terms are synonymous (e.g., see the abstracts for Djaldetti et al., Basic Res. Cardiol., 83:1435 (1988) and Gross et al., Arzheimittelforschung, 26:130 (1976); a copy of each is enclosed herewith).

Moreover, although the specification discloses that the bioavailability of DOXIL® to cell culture cells is unclear, as the active ingredient in DOXIL® is doxorubicin, in the context of the particular data disclosed in the specification (*in vitro* versus *in vivo*), one of skill in the art would understand the meaning of "DOX". That is, as DOXIL® is likely not bioavailable to culture cells, any positive response to "DOX" in cells *in vitro* would necessarily not be a response to DOXIL®. For example, the "DOX" employed to generate the data in Figures 7, 13, 17, and 19 was clearly not DOXIL®, as the data was obtained using HeLa cells, ferret fibroblasts, and A549 cells (Figures 7 and 13), and airway epithelial cells (Figures 17 and 19) *in vitro*. In contrast, the "DOX" employed to generate the data disclosed in Example 3C is clearly DOXIL® (note DOXIL® was administered intravenously). The data in Figure 18 was obtained after intranasal administration of rAAV and 200 μM Z-LLL and/or 200 μM Dox "as previously described in Duan et al. (2000)". Duan et al. (2000) administered doxorubicin, not DOXIL®. Moreover, regardless of the "DOX" formulation, the active agent in those formulations is doxorubicin.

Applicant's Representatives respectfully request clarification on the objection to the figure legend for Figure 4, as that legend was amended in the Amendment filed on August 14, 2007, to delete reference to co-administration.

The figure legends for Figures 6, 8, 9, 10, and 11 are amended, however, it is Applicant's position that prior to amendment, the data in these figures was clear. For example, it was clear which viruses were used and which agents were contacted with ferret fibroblasts in Figure 6, and it was clear which viruses and which agents were contacted with the apical surface of polarized airway epithelial cells and when data was collected in Figure 8. The Examiner is respectfully requested to more clearly articulate the alleged deficiencies in the figure legends for Figures 6 and 8-11 should the amendments herein be found not to address the objections to Figures 6 and 8-11.

With regard to the purported deficiency in the figure legend for Figure 13, Applicant's Representatives request guidance from the Examiner whether a substitute Figure 13, in which the left panel is marked as "A" and the right panel is marked as "B", would be remedial.

Thus, withdrawal of the objections to the specification is respectfully requested.

The 35 U.S.C. § 112, Second Paragraph, Rejections

Claims 1-2, 4-7, 9-24, 28, 43-44, 46, 48-50, and 54 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite, as the claims do not identify the correlation between the identity and structure of each agent and the effect achieved by that agent. Claims 21 and 43 were also rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for reciting a trademark. These rejections, as they may be maintained with respect to the pending claims, are respectfully traversed.

The amendment to claims 21 and 43 to delete "DOXIL" obviates the § 112(2) rejection over that term.

Claims 1 and 43 recite that at least two different agents are employed in an amount effective to at least additively enhance AAV transduction. Thus, it is clear that each agent alone enhances AAV transduction.

Accordingly, withdrawal of the § 112(2) rejections is respectfully requested.

The 35 U.S.C. § 112, First Paragraph, Rejections

Claims 1-2, 4-7, 9-24, 28, 43-44, 46, 48-50, and 54 were rejected under 35 U.S.C. § 112, first paragraph, as lacking adequate description. Claims 1-2, 4-7, 9-24, 28, 43-44, 46, 48-50, and 54 were also rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement. As these rejections may be maintained with respect to the pending claims, they are respectfully traversed.

In particular, with regard to an adequate written description, the Examiner asserts that DOXIL® is the only species whose complete structure is disclosed to be capable of altering the cellular uptake of rAAV, and LLnL is the only species whose complete structure is disclosed to be capable of modulating rAAV processing in the cell, and that the specification does not disclose any identifying characteristic as to how an artisan would have differentiated agents with those properties.

First, DOXIL® is not disclosed as being capable of altering the uptake of rAAV at the cell membrane (nor is LLnL, see page 10 of the Office Action).

Second, other agents useful in the methods of the invention are disclosed in the specification (see, for instance, the Examples).

Third, Duan et al. (J. Clin. Invest., 105:1573 (2000)), a reference cited against the claims under § 102, discloses methods to determine whether an agent alters cellular (membrane) uptake of AAV and whether an agent alters rAAV processing in the cell. Applicant need not teach what is well-known to the art. Hybritech Inc. v. Monoclonal Antibodies Inc., 802 F.2d 1367, 1379-80, 231 U.S.P.Q. 81, 84 (Fed. Cir. 1986).

To provide an adequate written description for a claimed genus, the specification can provide a sufficient description of a representative number of species by an actual reduction to practice, reduction to drawings or by a disclosure of relevant, identifying characteristics, i.e., by a structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics (Guidelines for Examination of Patent Applications under the 35 U.S.C. § 112(1) Written Description Requirement, Fed. Reg., 66, 1099 (2001)).

The agents recited in the claims are identified by relevant characteristics. For instance, one of the agents recited in claim 1 enhances AAV transduction and is a chemotherapeutic, a lipid lowering agent, an antibiotic or a tannic acid and the other agent, which also enhances AAV transduction, inhibits proteosome proteolytic activity. In claim 43, one of the recited agents that enhances AAV transduction is epoxomicin, doxorubicin, daunorubicin, idarubicin, epirubicin, aclarubicin, simvastatin or tannic acid and the other agent enhances AAV transduction after viral binding to the cellular membrane and before second strand synthesis which yields an expressible form of the viral genome.

Therefore, one of skill in the art would recognize that Applicant was in possession of the necessary common attributes or features of the elements possessed by members of the genus.

With regard to enablement, the Examiner asserts that a) the breadth of the claims is exceptionally large, encompassing methods of enhancing the transduction of an enormous genus of rAAV in an enormous genus of mammalian cells *in vitro* or *in vivo* with an enormous genus of structurally diverse agents and so it would require undue experimentation to practice the invention; b) the prior art teaches that most viral gene delivery systems utilized to date have demonstrated significant limitations in practicality and safety, citing Kapturczak et al. (Curr. Mol. Med., 1:245 (2001)) and Mah et al. (Molecular Ther., 6:106 (2001)); c) Goncalves (Virology J., 2:43 (2005)) teaches that the events and processes that regulate the trafficking of

AAV particles into the nucleus are not fully understood; d) Yan et al. (J. Virology, 78:2863 (2004)) teach that doxorubicin is an inhibitor of the chymotrypsin-like proteolytic activity of the 20S proteosome, which contradicts the agent elected species recited in claims 43 and 60; e) Duan et al. (J. Clin. Invest., 105:1573 (2000)) teach that the enhanced transduction of cells by rAAV observed in the presence of LLnL is not universal to all cells; and f) the proteasome modulating agent now claimed inhibits proteasome protease activity while the originally-filed disclosure discloses that the agent may modulate the proteosome, but does not inhibit proteolytic activity of the proteosome.

It is well-settled that it is not necessary that a patent applicant have prepared and tested all the embodiments of his invention in order to meet the requirements of § 112. In re Angstadt, 190 U.S.P.Q. 214, 218 (C.C.P.A. 1976). Furthermore, enablement is not precluded by the necessity for some experimentation, such as routine screening. The key word is "undue" not "experimentation." In re Angstadt, 190 U.S.P.Q. 214, 219 (C.C.P.A. 1976). In fact, a considerable amount of experimentation is permissible if it is merely routine, or the specification provides a reasonable amount of guidance with respect to the direction in which the experimentation should take. Ex parte Jackson, 217 U.S.P.Q. 804, 807 (Bd. App. 1982). Thus, if Applicant's invention is disclosed so that one of ordinary skill in the art can practice the claimed invention, even if the practice of the invention by the art worker includes routine screening or some experimentation, Applicant has complied with the requirements of 35 U.S.C. § 112, first paragraph. In re Angstadt, 190 U.S.P.Q. 214 (C.C.P.A. 1976); Ex parte Jackson, 217 U.S.P.Q. 804 (Bd. App. 1982).

With regard to the "enormous" genus of rAAV and "enormous" genus of mammalian cells, it is Applicant's position that it is well within the skill of the art, in view of Applicant's disclosure, to contact various isolates of AAV and a wide variety of mammalian cells with two or more agents, including the recited agent(s), to determine whether the agents at least additively enhance rAAV transduction.

In response to the undue experimentation alleged to be necessary to practice the invention, the Examiner simply cannot reasonably contend that a program to locate biomolecules with target biological or physical properties would not be carried out by the art because the results cannot be predicted in advance.

In fact, the Federal Circuit has explicitly recognized that the need, and methodologies required, to carry out extensive synthesis and screening programs to locate biomolecules with particular properties do not constitute undue experimentation. In re Wands, 8 U.S.P.Q.2d 1400, 1406-1407 (Fed. Cir. 1988), the Court stated:

> The nature of monoclonal antibody technology is that it involves screening hybridomas to determine which ones secrete antibody with desired characteristics. Practitioners of this art are prepared to screen negative hybridomas in order to find one that makes the desired antibody.

Likewise, practitioners in the art related to the present application would be well-equipped to prepare and/or screen combinations of agents falling within the scope of the claims to identify those agents that at least additively enhance AAV transduction. See also, Hybritech Inc. v. Monoclonal Antibodies Inc., 231 U.S.P.Q. 81, 84 (Fed. Cir. 1986) (evidence that screening methods used to identify characteristics [of monoclonal antibodies] were available to art convincing of enablement). Thus, the fact that a given claim may encompass a variety of agents, mammalian cells and AAVs is not dispositive of the enablement issue, particularly in an art area in which the level of skill is very high and in which screening of large numbers of compounds has been standard practice for at least ten years (Ex parte Forman, 230 U.S.P.Q.2d 456 (Bd. App. 1986).

As the claims recite particular agent combinations and the specification teaches how to identify agents useful in the claimed methods, based on the skill of the worker in the relevant art and Applicant's disclosure, that identification would not require undue experimentation.

Kapturczak et al. disclose that rAAV offers a vehicle for safe, long-term therapeutic gene transfer and note that substantial progress has been made in addressing AAV related issues, such as packaging capacity, packaging systems, and the availability of virus receptors on some cell types. For instance, to overcome subtherapeutic levels of transduction after systemic delivery, Mah et al. disclose modifying AAV2 virions with microspheres.

Moreover, while the process regulating AAV trafficking into the nucleus may not be fully understood (Goncalves), the specification discloses that agents that modulate that process may be useful in the claimed methods. The enablement requirement of § 112(1) does not require that

Applicant fully understand any process but does require that the specification teach how to make and use the claimed invention.

None of Kapturczak et al., Mah et al. or Goncalves relate to the use of exogenously administered agents to enhance AAV transduction and so do not evidence the level of (or lack of) predictability in the relevant art.

There is no contradiction between Yan et al. and the present disclosure, as Yan et al. disclose that doxorubicin interacts with the proteasome through a mechanism distinct from that of tripeptidyl aldehydes. Yan et al. do refer to the work of others, which reported that doxorubicin inhibits proteasome activity in a manner similar to aclarubicin.
However, the Examiner is requested to note that the present specification discloses that "proteosome modulating agents" do not include agents that inhibit the proteolytic activity of the proteosome, that doxorubicin may facilitate viral binding to the proteasome and/or subsequent transportation into the nucleus in contrast to proteasome inhibitors such as LLnL and Z-LLL, and that the combined use of agents that individually have different or overlapping properties that alter rAAV transduction, as well as agents with similar or identical properties, can result in an additive and/or synergistic effect (pages 7-9).

Finally, the fact that certain agents are not as effective in enhancing AAV transduction in some cells types relative to other cell types (Duan et al.) is irrelevant to whether the specification enables the claimed invention. Moreover, as discussed in Goncalves and Mah et al., AAV virions can be modified to include targeting moieties, and those moieties may enhance AAV uptake into cells that have few AAV receptors.

Therefore, withdrawal of the § 112(1) rejections is respectfully requested.

The 35 U.S.C. § 102 Rejection

Claims 1-2, 4, 5-7, 9, 16, 18, 21-23, and 28 were rejected under 35 U.S.C. § 102(b) as being anticipated by Duan et al. (J. Clin. Invest., 105:1573 (2000)). The amendment to claim 1 to delete "food additive" renders moot the § 102(b) rejection. Accordingly, withdrawal of the § 102 rejection is respectfully requested.

The 35 U.S.C. § 103 Rejections

Claims 1, 10-17 and 19-20 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Duan et al. and Englehardt et al. (U.S. Patent No. 6,436,392). Claims 1 and 24 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Duan et al. and Englehardt et al., and in further view of Hirsch et al. (U.S. published application No. 2003/0003583). Claims 43-44, 46, 48-50, and 54 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Duan et al. in view of Kiyomiyo et al. (Cancer Res., 61:2467 (2000)). These rejections are respectfully traversed.

Duan et al. disclose that the combined effects of EGTA and LLnL on AAV transduction might be due to reduced degradation of internalized virus and an increased rate of endocytosis, and that the combination enhanced the amount of virus internalized from apical surfaces (page 1583). As LLnL does not alter AAV binding to cell surfaces or internalization (page 1581), it is likely EGTA altered AAV binding to cell surfaces or internalization, i.e., EGTA is not an inhibitor of proteosome proteolytic activity. In addition, EGTA is not a chemotherapeutic, lipid lowering agent, antibiotic or tannic acid.

It is disclosed in the '392 patent that rAAV vectors, each containing a promoter and an open reading frame between ITRs, may become linked after infection of the host cell with the vectors and synthesis of double-stranded viral DNA (column 4, lines 41-56 and column 5, lines 26-38). Other vectors disclosed in the '392 patent include rAAV vectors that contain an open reading frame flanked by a splice site, i.e., one rAAV vector contains a splice acceptor site and another rAAV vector contains a splice donor site, which vectors together encode a functional gene product (column 4, lines 57-column 5, line 25). It is disclosed that transcription of a molecule formed by linking the two rAAVs in a cell results in a spliced RNA molecule which encodes a functional peptide (column 49, lines 14-22).

The '392 patent is not concerned with administering agents that enhance AAV transduction. Thus, the '392 patent does not remedy the deficiencies of Duan et al.

Hirsch et al. disclose the regulation of transgene expression following AAV transduction, where expression is regulated by a proteosome inhibitor (abstract). The data in Hirsch et al. is based on the use of the proteosome inhibitor Z-LLL, although other proteosome inhibitors are

disclosed in paragraphs 0119-0125. There is nothing in Hirsch et al. to suggest the use of any other agents to alter AAV transduction.

Kiyomiyo et al. disclose a mechanism for the nuclear transport of adriamycin, which may involve binding of adriamycin to the 20S proteosome. There is nothing in Kiyomiyo et al. related to virus transduction.

Thus, there is no combination of the cited documents that discloses or suggests the use of the recited combination of agents and, given the disclosure of agents that likely interact with proteosomes in Duan et al., Hirsch et al., and Kiyomiyo et al., it is unexpected that a combination of agents with purportedly the same target would at least additively enhance AAV transduction, as those agents would be expected to be competitors. Moreover, in the absence of Applicant's disclosure, there is nothing in the cited art that would motivate one of skill in the art to select the recited agents (which unlike EGTA do not enhance AAV uptake at the cell membrane) to enhance AAV transduction.

Therefore, withdrawal of the § 103 rejections is respectfully requested.

CONCLUSION

Applicant respectfully submits that the claims are in condition for allowance, and notification to that effect is earnestly requested. The Examiner is invited to telephone Applicant's attorney at (612) 373-6959 to facilitate prosecution of this application.

If necessary, please charge any additional fees or credit overpayment to Deposit Account No. 19-0743.

Respectfully submitted,

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by First Class Mail, postage prepaid,

CERTIFICATE UNDER 37 CFR 1.8: The undersigned hereby certifies that this correspondence is being filed ~~using the USPTO's electronic filing system EFS-Web, and is~~ addressed to: Mail Stop Amendment, Commissioner of Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on this 31 day of January 2008.

CANDIS BUENDING _____

Name Signature

1: Basic Res Cardiol. 1988 Nov-Dec;83(6):672-7.

Links

SEM observations on the effect of anthracycline drugs on cultured newborn rat cardiomyocytes.

Djaldetti M, Gilgal R, Shainberg A, Klein B, Zahavi I.

Department of Medicine B, Hasharon Hospital, Petah-Tiqva, Israel.

The effect of two anthracyclines-doxorubicin hydrochloride (adriamycin) and 4'-epidoxorubicin (epirubicin) and an anthracenedione (novantrone) on the contractibility and surface ultrastructure of newborn rat cardiomyocytes cultured for five days was examined. While the beating rate of the cells was affected only by the anthracyclines, an alteration of the sarcolemma, disruption of the slender processes and swelling of the nuclei and/or the cells was observed following incubation with each of the three drugs for two hours. However, the damage induced by adriamycin was more pronounced than that induced by the other two drugs, when doses extrapolated from those accepted as therapeutic were compared.

PMID: 3223881 [PubMed - indexed for MEDLINE]

Note: Performing your original search, ***doxyrubicin and adriamycin***, in PubMed will retrieve *6* citations.

1: Arzneimittelforschung. 1976;26(1A):130-5.

[Clinical problems of optimum bioavailability, in particular in cytostatic therapy (author's transl)]

[Article in German]

Gross R, Hirschmann WD.

The clinical application of cytostatic drugs requires knowledge of their biochemistry, pharmacology, pharmacokinetics as well as their action at the cellular level within the generation cycle. The principles apply to tumor cells as well as to normal, rapidly proliferating tissues. The intensive research on cancer treatment all over the world is leading to a rapid accumulation of experimental data about the action of single cytostatic drugs in tissue culture and on transplantable animal tumor systems, especially in rodents. Clinical chemotherapy in human malignancies today preferentially uses combinations of different cytostatics. Inumerable combinations of drugs are available, especially if variations in respect to drug dose and intervals of drug application are taken into consideration. The experimental basis for such combinations of drugs and drug interactions is scanty. Using the pyrimidine analog cytosine arabinoside and the two antibiotics daunorubicin and doxyrubicin (adriamycin) as examples, it is demonstrated that information on the pharmacolinetic behaviour of cytostatic drugs is a prerequisite for their success in clinical application, but is on its own insufficient to predict the tumor response.

PMID: 947192 [PubMed - indexed for MEDLINE]